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Janet D'Annunzio-Ellis

Printed name of person mailing correspondence

Jacob D'annuage Elles

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Gary Ruvkun et al.

Art Unit:

1632

Serial No.:

08/908,453

Examiner:

Ram R. Shukla

Filed:

August 7, 1997

Customer No.:

21559

Title:

AGE-1 POLYPEPTIDES AND RELATED MOLECULES AND

METHODS

Mail Stop Appeal Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450.

<u>APPEAL BRIEF</u> SUBMITTED PURSUANT TO 37 CFR § 41.37

In support of Appellants' Notice of Appeal filed October 3, 2005 of the Office's final rejection mailed on March 31, 2005, submitted herewith is Appellants' Appeal Brief.

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Exhibit A filed November 17, 2003 and entered March 31, 2005¹ Exhibit B filed November 17, 2003 and entered March 31, 2005 Exhibit C filed November 17, 2003 and entered March 31, 2005

¹ In the Interview Summary mailed September 30, 2005, Examiner Shukla states that the papers filed on November 17, 2003 were considered by the Examiner while preparing the Office Action of March 31, 200<u>3</u>. Appellants submit that the Office Action referred to is the one mailed on March 31, 200<u>5</u>.

Real Party in Interest

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The Real Party in Interest is The General Hospital Corporation, to which all interest in the present application has been assigned by virtue of an Assignment, recorded on July 23, 1998 (Reel/Frame 9334/0514).

Related Appeals and Interferences

There are no currently pending appeals or interferences related to this case.

Status of Claims

Claims 8, 10-13, 15, 16, 19, and 20 are currently pending. Claims 1-7, 14, and 21-28 are withdrawn from consideration. Claims 9, 17, 18, 29, and 30 were canceled Claims 8, 10-13, 15, 16, 19, and 20 were finally rejected in a Final Office Action mailed on March 31, 2005, and are appealed.

Status of Amendments

All amendments have been entered and are reflected in the appended claims.

Summary of the Invention

Appellants' invention generally features a purified and isolated DNA encoding an AGE-1 polypeptide having PI-3 kinase activity, and methods of identifying compounds that decrease AGE-I expression or biological activity. Specifically, the claims on appeal are directed to the following compositions and methods:

- (i) purified and isolated DNA encoding an AGE-1 polypeptide containing SEQ ID NO:1 (claim 8), and vectors and cells that include this DNA (claims 10 and 11, respectively);
- (ii) methods of producing a recombinant AGE-1 polypeptide using the vectors and cells of the invention and recombinant polypeptides produced by such methods (claims 12 and 13, respectively);

(iii) screening methods for candidate compounds that require (a) a nematode cell expressing its endogenous AGE-1 DNA; (b) contacting the nematode cell with a candidate compound; and (c) measuring AGE-1 gene expression in the nematode cell, a decrease in AGE-1 gene expression following contact with the candidate compound, compared to AGE-1 gene expression in a nematode cell that is not contacted with the candidate compound, identifying the candidate compound as a compound that is capable of decreasing AGE-1 gene expression (claims 15, 19, and 20); and

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(iv) screening methods for candidate compounds that require (a) a cell expressing a recombinant AGE-1 polypeptide; (b) contacting the cell with a candidate compound; and (c) measuring the PI 3-kinase activity of the cell, a decrease in AGE-1 PI 3-kinase activity of the cell following contact with the candidate compound, compared to AGE-1 PI 3-kinase activity in a cell that is not contacted with the candidate compound, identifying the candidate compound as a compound that is capable of decreasing AGE-1 PI 3-kinase activity (claims 16, 19, and 20).

Each of these claims is described in the specification. The amino acid sequence of an AGE-1 polypeptide, for example, is found at Figure 3 (SEQ ID NO:1), and the nucleic acid sequence of an AGE-1 cDNA is found at Figure 4. Cells and vectors containing a nucleic acid encoding an AGE-1 polypeptide and methods of using these cells and vectors for the production of recombinant AGE-1 polypeptides are provided at pages 28-29.

Methods for screening candidate compounds are provided in Appellants' specification at page 31, line 7 to page 34, line 7. In particular, at page 31, lines 15-17, Appellants teach methods for measuring AGE-1 expression. At page 31, lines 9-14, Appellants teach that AGE-1 expression may be measured following the addition of antagonist molecules either to culture medium or to an animal, for example, a nematode, and, at page 31, lines 17-19, Appellants teach that the level of AGE-1 expression in the presence of a candidate molecule is compared to the level measured for the same cells in the absence of the candidate molecule. In addition, Appellants teach methods for identifying compounds that modulate AGE-1 kinase activity *in vitro* at page 32, lines 8-

21. Methods for the selection of candidate compounds are provided at page 31, lines 19-21, and methods for purifying such compounds are provided at page 32, lines 1-7. Appellants teach that the usefulness of compounds that modulate AGE-1 expression can be confirmed by testing the compounds in animal models such as nematodes (page 33, lines 4 and 5). Finally, at page 33, lines 6-9, Appellants teach that selected compounds may be used as therapeutics to decrease the level of native AGE-1 expression and thereby increase the longevity of an animal, for example, a human.

Issues on Appeal

This appeal presents two issues:

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- I. Whether the Office erred in rejecting claims 8, 10, and 11 as being anticipated by Swinburne (EMBL Accession No. Z66519, October 27, 1995); and
- II. Whether the Office erred in rejecting claims 8, 10-13, 15, 16, 19, and 20 as being obvious over Swinburne (EMBL Accession No. Z66519, October 27, 1995) in view of Johnson et al. (Genetica 91:65-77, 1993).

Arguments

The present anticipation and obviousness rejections are based on a central factual error that requires reversal. As is discussed below, these rejections turn on a primary reference by Swinburne and the assertion that this reference disclosed Appellants' AGE-1 amino acid sequence prior to Appellants' priority application filing date of August 7, 1996. This assertion is incorrect. The sequence provided by Swinburne was updated on multiple occasions from its initial submission in October 1995. As of Appellants' filing date, Swinburne had not submitted a full-length AGE-1 sequence, nor identified its function. This reference therefore cannot anticipate or render obvious Appellants' claims to the AGE-1 sequence of SEQ ID NO:1 or methods for identifying AGE-1 modulatory compounds that measure changes in its gene expression or PI-3 kinase activity. The rejections based on Swinburne must be reversed.

I. The Swinburne Reference Does Not Teach the Claimed Invention

The case law is clear that, to anticipate a claim, a prior art reference must disclose, either expressly or inherently, all of the limitations of the claim. *Kalman v. Kimberley-Clark Corp.*, 713 F.2d 760, 218 U.S.P.Q. 781 (Fed. Cir. 1983).

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As indicated above, claim 8 is directed to purified and isolated DNA encoding an AGE-1 polypeptide that includes the sequence of SEQ ID NO:1, and claims 10 and 11 are directed to a vector and cell, respectively, that include that purified and isolated AGE-1 DNA. The Office has rejected these claims under 35 U.S.C. § 102(a) as being anticipated by Swinburne (GenBank Accession No. Z66519), asserting that this GenBank submission disclosed the amino acid sequence of SEQ ID NO: 1 as of October 27, 1995. This assertion is in error.

While it is true that the first Swinburne sequence submission occurred in October 1995,² the nucleic acid sequence of the cosmid "B0334" that is the subject of the submission underwent continual updating since it first became available. Exhibit A to Appellants' Reply filed November 17, 2003 (and considered by the Examiner in the preparation of the March 31, 2005 Office Action) provides a sequence revision history, indicating that this submission was updated multiple times following Appellants' priority application filing date of August 7, 1996. Exhibit B to Appellants' Reply filed November 17, 2003 provides the version of Gene Bank Accession No. Z66519 available as of July 29, 1996, a deposit made just prior to the filing of Appellants' priority document (U.S.S.N. 60/023,382). As shown in Exhibit B, at page 4, as of July 29, 1996, the polypeptide product of B0334.8 contained just *seventy-six* amino acids.³ In contrast, the AGE-1 polypeptide sequence of SEQ ID NO:1 contains *one thousand one hundred forty-six* amino acids. Thus, contrary to the Office's assertion, the cited Swinburne reference Z55419 [gi:1044812] -- available as of Appellants' priority application filing date -- clearly does *not* disclose SEQ ID NO:1 and cannot anticipate Appellants' claims.

² The GenBank submission history indicates that this sequence was "first seen at NCBI on October 30, 1995," not October 27, 1995 as indicated by the Office. Appendix A to Appellants' Reply filed November 17, 2003 and considered March 31, 2005.

In fact, contrary to the Office's assertion, the nucleic acid sequence of AGE-1 was *not* publicly available at the time Appellants' patent application was filed. This point is made clear in Appellants' specification at page 20, lines 1-7, where Appellants state:

The *C. elegans* Genome Project has sequenced cosmid B0334. Analysis of the DNA sequence in the 4 kb region that detected the *age-1(mg55)* breakpoint revealed two putative exons that showed strong sequence identity with the last 88 amino acids of mammalian phosphatidylinositol 3-kinase (PI 3-kinase) p110 catalytic subunit. *The region to the right of B0334 expected to contain the rest of age-1 was not cloned in cosmids or phage by the C. elegans genome project* (emphasis added; citations omitted).

Appellants, and not Swinburne, were the first to obtain the *age-1* nucleic acid and amino acid sequences, as evidenced by Appellants' specification at page 20, lines 7-17.

We isolated genomic phage and cDNA clones extending to the right from B0334 and used anchored polymerase chain reaction (PCR) of reverse transcribed RNA to isolate and determine the sequence of the coding region of age-1 (Figure 2C). To confirm the splicing pattern of age-1, reverse transcription PCR (RTPCR) was used in conjunction with genomic sequencing of predicted splice junctions. The sequence predicted by cDNA clones and anchored PCR was further confirmed by sequencing genomic fragments corresponding to the predicted coding sequence. Because three independent cDNA clones end within 30 base pairs of each other and because these encode a protein coextensive with mammalian p110 (see below), we concluded that the assembled age-1 cDNA was likely to be complete. The nucleic acid sequence of the C. elegans age-1 cDNA is shown in Figure 4.

Indeed, if the age-1 nucleic acid sequence was publicly available, Appellants would not have gone to the trouble of cloning and sequencing the gene.

It is clear that Swinburne, as of Appellants' priority application filing date, failed to disclose a nucleic acid sequence encoding SEQ ID NO:1, as required by claims 8, 10, and 11. The anticipation rejection in this case has been maintained in error; it should be reversed.

³ Evidence that cosmid B0334.8 encodes AGE-1 is provided by Exhibit C to Appellants' Reply filed November 17, 2003 (and considered March 31, 2005), under the heading "Definition."

II. Swinburne and Johnson, in Combination, Do Not Suggest the Claimed Invention

To establish a *prima facie* case of obviousness under § 103, the Examiner must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. *See* 35 U.S.C. § 103(a) (Supp. III 1997); *In re Dembiczak*, 175 F.3d 994, 998, 50 U.S.P.Q.2d 1614, 1616 (Fed. Cir. 1999), *abrogated on other grounds by In re Gartside*, 203 F.3d 1305, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). Whether or not a claimed invention would have been obvious is a "legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness." *Id*.

Claims 8, 10-13, 15, 16, 19, and 20 feature compositions requiring the AGE-1 amino acid sequence of SEQ ID NO:1 and methods of identifying modulatory compounds that depend on measurement of AGE-1 gene expression or PI-3 kinase activity. These claims stand rejected under 35 U.S.C. § 103 as obvious over Swinburne (Gene Bank Accession No. Z66519) in view of Johnson et al. (Genetica 91:65-77, 1993) based on the Office's assertion that:

... it would have been obvious for an artisan of skill to express the DNA of Swinburne in a cell and express the protein in a cell, isolate the protein and study its function or practice method of identifying compounds that decrease the expression of Age-1 by following the method of Johnson et al and routine cell culture methods. An artisan of skill would have been motivated to express Age-1 in a cell, isolated Age-1 protein and tested its activity because Swinburne identified putative functional domain.

Additionally, an artisan would have been motivated to practice the screening methods for identifying compounds that decrease Age-1 activity because Johnson et al teaches that molecular cloning and characterization of Age-1 locus will provide significant insights into the molecular basis of senescence (emphasis added). (Office Action mailed March 31, 2005, page 3, fourth paragraph.)

This rejection should similarly be reversed.

As detailed above, as of Appellants' priority application filing date, Swinburne failed to disclose the amino acid sequence of SEQ ID NO:1. Swinburne, as of that same date, also failed to disclose the nucleic acid sequence encoding SEQ ID NO:1; failed to identify *any* functional domain of AGE-1; and even failed to disclose that the *age-1* gene was present on cosmid B0334. Swinburne therefore does not teach what the Office asserts and does not suggest the invention of any of claims 8, 10-13, 15, 16, 19, or 20.

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In addition, the secondary reference, Johnson, fails entirely to remedy the deficiencies of Swinburne. Johnson merely describes the effects of an *age-1* mutation on lifespan and maps *age-1* to somewhere on chromosome II. Johnson does not provide the skilled artisan with the information, requisite motivation, or expectation of success required to obtain a nucleic acid sequence encoding SEQ ID NO:1, to express it in a cell, or to identify any functional domains.

Appellants were the first to genetically map, clone, and sequence *age-1* as evidenced by Appellants' specification. Appellants carried out three-factor mapping, deficiency mapping, physical mapping, breakpoint analysis, and anchored polymerase chain reaction of reverse transcribed RNA to isolate and sequence the *age-1* coding region (pages 19-21, Figures 2A, 2B, 2C). The *age-1* amino acid and nucleic acid sequences first obtained by Appellants are shown in Figures 3 and 4, respectively. Appellants were the first to molecularly characterize mutant alleles of *age-1* (page 20, line 24, to page 21, line 7); were the first to appreciate that *age-1* encodes a phosphatidylinositol 3-kinase (page 21, line 3, to page 22, line 25); and were the first to appreciate that a decrease in AGE-1 activity would directly increase lifespan (page 22, line 26, to page 23, line 23). The references cited by the Office uniformly fail to recognize these key insights, in addition to failing to provide the AGE-1 sequence.

The obviousness rejection in this case has also been maintained in error, and should be reversed.

Conclusion

Appellants respectfully request that the rejection of claims 8, 10-13, 15, 16, 19, and 20 be reversed. Enclosed is a check in the amount of the required fee set forth in 37 C.F.R. § 41.20(b)(2) for filing the present Appeal Brief.

If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 29 November 2005

Karen L. Elbing, Ph.Z.

Reg. No. 35,238

Clark & Elbing LLP 101 Federal Street Boston, MA 02110

Telephone: 617-428-0200 Facsimile: 617-428-7045

Claims Appendix

- 8. A purified and isolated DNA which encodes an AGE-1 polypeptide, said polypeptide comprising the sequence of SEQ ID NO: 1.
 - 10. A vector comprising the purified and isolated AGE-1 DNA of claim 8.
 - 11. A cell comprising the purified and isolated AGE-1 DNA of claim 8.
- 12. A method of producing a recombinant AGE-1 polypeptide, said method comprising the steps of:
- (a) providing a cell transformed with the DNA of claim 8 encoding an AGE-1 polypeptide, said DNA being expressed in the cell;
 - (b) culturing the transformed cell under conditions for expressing the DNA; and
 - (c) isolating the recombinant AGE-1 polypeptide.
- 13. A recombinant AGE-1 polypeptide produced according to the method of claim 12.
- 15. A method of identifying an AGE-1 modulatory compound that is capable of decreasing the expression of an AGE-1 gene, said method comprising the steps of:
 - (a) providing a nematode cell expressing its endogenous AGE-1 DNA,
 - (b) contacting said nematode cell with a candidate compound; and
 - (c) measuring AGE-1 gene expression in said nematode cell, a decrease in AGE-1 gene expression in said nematode cell following contact with said candidate compound, compared to AGE-1 gene expression in a nematode cell that is not contacted with said candidate compound, identifying said candidate compound as a compound that is capable of decreasing AGE-1 gene expression.

- 16. A method of identifying an AGE-1 modulatory compound that is capable of decreasing AGE-1 PI 3-kinase activity, said method comprising the steps of:
 - (a) providing a cell expressing an AGE-1 polypeptide of claim 8;
 - (b) contacting the cell with a candidate compound; and
- (c) measuring the PI 3-kinase activity of said cell, a decrease in AGE-1 PI 3-kinase activity of said cell following contact with the candidate compound, compared to AGE-1 PI 3-kinase activity in a cell that is not contacted with said candidate compound, identifying said candidate compound as a compound that is capable of decreasing AGE-1 PI 3-kinase activity.
- 19. The method of claim 15 or 16, wherein said method is carried out in a nematode
- 20. The method of claim 15 or 16, wherein said method involves assaying AGE-1 PI 3-kinase activity *in vitro*.

Evidence Appendix

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EXHIBIT A



Sequence Revision History

Structure

PMC

Taxonomy

OMIM

Book Čle

Find (Accessions, GI numbers or Fasta style SeqIds) Z66519

About Entrez

Show difference between I and II as GenBank/GenPept

Entrez

Search for Genes LocusLink provides curated information for human, fruit fly, mouse, rat, and zebrafish

Help | FAQ

Batch Entrez: Upload a file of GI or accession numbers to retrieve protein Or nucleotide sequences

Check sequence revision history

How to create WWW links to Entrez

LinkOut

Cubby

Related resources

BLAST

Reference sequence project

LocusLink

Clusters of orthologous groups

Protein reviews on the web

Revision history for **Z66519**

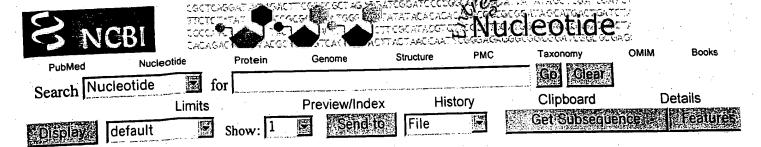
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	2	May 22 2003 11:12	Dead	C	0	_
18369669	2	Apr 27 2003 11:09	Dead	<u> C</u>	10	_
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1044812	1	Jun 23 2001 12:07	Dead		c	\overline{c}
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1044812		Jun 13 1998 3:34	Dead		10	10

EXHIBIT A

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Accession Z66519 was first seen at NCBI on Oct 30 1995 2:27

<u>Disclaimer | Write to the Help Desk</u> <u>NCBI | NLM|NIH</u>



1: Z66519[gi:1044812] This record was replaced or removed. See <u>revision history</u> for details.

INV 2.7-JUL-1996 linear 41812 bp DNA LOCUS Caenorhabditis elegans cosmid B0334. DEFINITION 266519 ACCESSION Z66519 GI:1044812 Gonadotrophin-releasing hormone receptor like protein; oxalyl-CoA VERSION KEYWORDS decarboxylase; Phytoene synthase precursor; potassium channel protein; Yeast hypothetical protein L8167.12 like protein. Caenorhabditis elegans SOURCE Caenorhabditis elegans ORGANISM Eukaryotae; mitochondrial eukaryotes; Metazoa; Nematoda; Secernentea; Rhabditia; Rhabditida; Rhabditina; Rhabditoidea; Rhabditidae; Caenorhabditis. (bases 1 to 41812) REFERENCE Swinburne, J. AUTHORS Direct Submission Submitted (26-OCT-1995) Nematode Sequencing Project, Sanger Centre, TITLE **JOURNAL** Hinxton, Cambridge CB10 1RQ, England and Department of Genetics, Washington University, St. Louis, MO 63110, USA. E-mail: jes@sanger.ac.uk or rw@nematode.wustl.edu (bases 1 to 41812) REFERENCE Wilson, R., Ainscough, R., Anderson, K., Baynes, C., Berks, M., **AUTHORS** Bonfield, J., Burton, J., Connell, M., Copsey, T., Cooper, J., Coulson, A., Craxton, M., Dear, S., Du, Z., Durbin, R., Favello, A., Fulton, L., Gardner, A., Green, P., Hawkins, T., Hillier, L., Jier, M., Johnston, L., Jones, M., Kershaw, J., Kirsten, J., Laister, N., Latreille, P., Lightning, J., Lloyd, C., McMurray, A., Mortimore, B., O'Callaghan, M., Parsons, J., Percy, C., Rifken, L., Roopra, A., Saunders, D., Shownkeen, R., Smaldon, N., Smith, A., Sonnhammer, E., Staden, R., Sulston, J., Thierry-Mieg, J., Thomas, K., Vaudin, M., Vaughan, K., Waterston, R., Watson, A., Weinstock, L.,

Wilkinson-Sproat, J. and Wohldman, P.

TITLE 2.2 Mb of contiguous nucleotide sequence from chromosome III of C. elegans

JOURNAL Nature 368 (6466), 32-38 (1994)

MEDLINE 94150718

COMMENT

Current sequence finishing criteria for the C. elegans genome sequencing consortium are that all bases are either sequenced unambiguously on both strands, or on a single strand with both a dye primer and dye terminator reaction, from distinct subclones. Exceptions are indicated by an explicit note.

IMPORTANT: This sequence is NOT necessarily the entire insert of clone B0334. It may be shorter because we only sequence overlapping sections once, or longer because we arrange for a small overlap between neighbouring submissions.

The true left end of clone B0334 is at 1 in this sequence. The true right end of clone B0334 is at 41812 in this sequence. Coding

```
sequences below are predicted from computer analysis, using the
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            available information.
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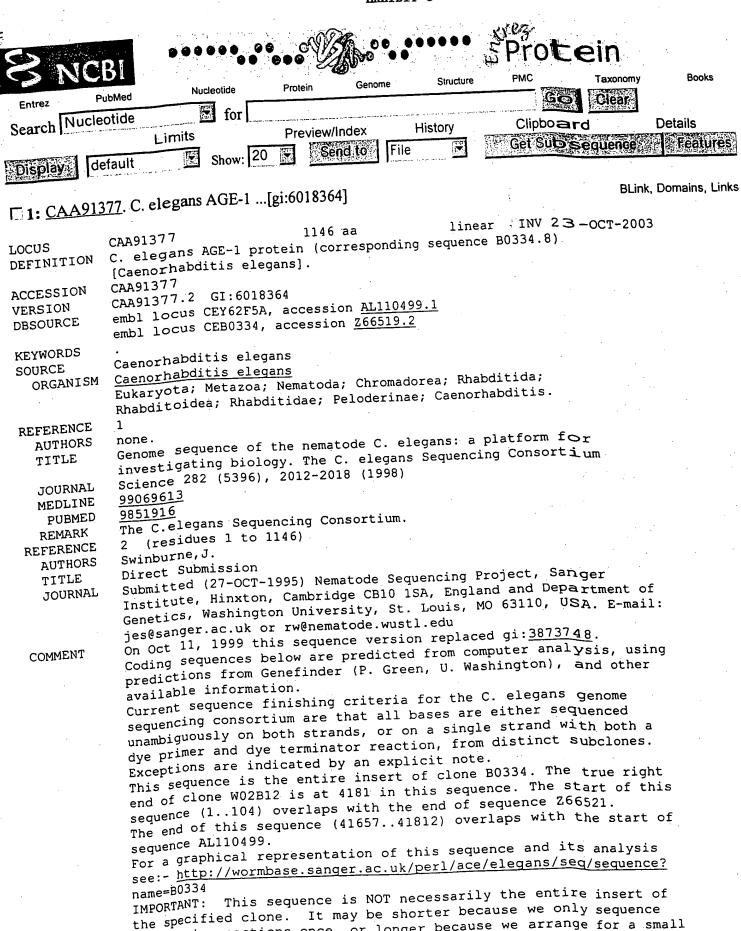
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EXHIBIT C

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Nov 3 2003 07:26:36